

Public  
health seriesSeries editor  
Graham NeilsonControl of STDs—the role of prophylactic  
vaccines against herpes simplex virus

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**Objectives:** To summarise the current status of genital herpes simplex virus (HSV) vaccine development and provide a discussion of the potential benefits and limitations of genital herpes vaccines.

**Methods:** Literature review.

**Results:** Genital herpes simplex virus infection has a complex pathogenesis that has contributed to it becoming a serious worldwide problem. In an attempt to control the problem five different types of genital herpes vaccines have been developed. These include inactivated virion derived vaccines, adjuvanted subunit vaccines, vectored vaccines, replication limited live viral vaccines, genetically attenuated live viral vaccines, and nucleic acid vaccines. While available commercially in some parts of the world, inactivated virion derived vaccines have not been proved effective. Of the others, adjuvanted subunit vaccines, replication limited live viral vaccines, and nucleic acid vaccines are currently in clinical trials and vectored vaccines and genetically attenuated live viral vaccines are in preclinical development.

**Conclusion:** With regard to HSV vaccines in general, it is reasonable to expect that the newer vaccines may protect the individual from developing symptomatic genital herpes but may not protect against asymptomatic viral infection. With widespread use HSV vaccines might help to prevent the spread of genital herpes.

(Sex Transm Inf 1998;74:391–394)

Keywords: genital herpes; herpes vaccines; herpes simplex virus

## Introduction

Genital herpes is a common sexually transmitted disease (STD) that occurs throughout the world.<sup>1,2</sup> Either herpes simplex virus (HSV) type 1 or 2 may cause it. Infection is chronic and lifelong and manifested by recurrent episodes of vesicular and/or ulcerative lesions on or about the genitalia. While seldom life threatening it can have significant consequences for many people as summarised in table 1. Recent data from the United States and the United Kingdom suggest that the number of people with genital herpes continues to increase despite the promotion of safe sex practices and the availability of effective antiviral therapy.<sup>3,4</sup> Given the expanding problem posed by genital herpes and the chronic nature of the infection the development of an effective vaccine would seem the most logical strategy for controlling this common disease. There are several different HSV vaccines currently in development. However, the complex natural history of HSV infection makes effective control of genital herpes a daunting task.

## Pathogenesis

Some knowledge regarding the pathogenesis of HSV infection is important for understanding how a vaccine might affect the spread of genital herpes.<sup>5,6</sup> Following genital to anogenital or oral to anogenital transmission of virus the infection begins with HSV replication at mucosal or cutaneous sites. Virus rapidly enters sensory nerve endings and is transported within nerve fibres to sensory neurons within sacral dorsal root ganglia. In some cases virus also spreads to the spinal cord where replication can cause neurological injury resulting in urinary retention or meningitis. After replicating in sensory neurons newly produced virions spread from the ganglia via nerve fibres back to mucocutaneous sites in the anogenital area, where further replication in epithelial cells results in the formation of herpetic vesicles and ulcers. Based on animal studies it is thought that the characteristic vesiculo-ulcerative lesions do not result from local replication of the transmitted virus, but rather develop as a consequence of the virus that reaches skin and mucosal surfaces through neuronal spread.<sup>5,6</sup> In time, host immune responses limit viral replication and terminate the infection. Some virus, however, escapes immune mediated destruction by persisting in a non-replicating state within sensory neurons. Once established, latent infection persists for the life of the host and is not affected by antiviral drugs such as aciclovir that act only on replicating virus. Latent infection itself is thought to cause no pathology but reactivation of a latently infected neuron causes the latent virus to begin replicating and producing progeny virus. The reactivated virus spreads via nerve fibres to

Table 1 Major consequences of genital herpes

Pain and discomfort associated with genital lesions
Systemic complications such as urinary retention or aseptic meningitis
Psychological morbidity related to anticipating recurrences
Psychological morbidity related to fear of transmission to a susceptible partner or fetus/neonate
Rare complication of disseminated infection almost exclusively seen in the immunocompromised host
Rare complication of perinatal transmission resulting in potentially life threatening neonatal infection
Increased risk of acquiring HIV infection if exposed

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Accepted for publication  
8 October 1998

Table 2 Types of HSV vaccines

Vaccine type	Example	Status of vaccine type
Inactivated virion derived vaccines	Skinner vaccine	These vaccines are effective in experimental models but clinical trials have failed to establish their effectiveness in humans.
Adjuvanted subunit vaccines	gD2/MPL, SmithKline Beecham	In phase III clinical trials the Chiron HSV-2 gB/gD/MF59 vaccine failed; results of a large trial of the SmithKline HSV-2 gD/MPL vaccine are expected in 1998 or 1999.
Vectored vaccines	gD2/varicella zoster virus	Immunogenic and modestly effective in animals but vectored have not yet entered clinical testing.
Replication limited live viral vaccines	DISC-HSV, Cantab	Effective in animals, phase I clinical testing show that the DISC-HSV vaccine is safe and immunogenic. Phase II/III studies are planned.
Genetically attenuated live viral vaccines	RAV 9395, Aviron	Effective in experimental models but issues regarding safety remain a concern.
Nucleic acid vaccines	Facilitated gD2 - Apollon	Effective in experimental models, a phase I clinical trial is under way.

anogenital sites where further virus replication occurs resulting in what is termed recurrent infection. Recurrent infections may be symptomatic with clinically apparent vesicles, ulcers, or other recognisable signs and symptoms, or they may be asymptomatic characterised only by shedding of virus from anogenital sites. Animal studies suggest that the magnitude of the latent infection is established during the initial infection and that the greater the burden of latent virus the more frequent the recurrent infections.

#### Vaccine expectations

To protect completely against genital herpes a vaccine will need to induce a durable immunity that prevents infection at the mucosal or cutaneous portal of virus entry. Such a "sterilising immunity" would prevent infection by blocking virus replication in epithelial cells and preventing HSV entry into the peripheral nervous system. Prevention of infection, however, may not be a feasible goal. In animal studies vaccine induced immunity has not prevented viral replication in the genital tract nor the establishment of latent infection in sensory ganglia after experimental HSV challenge.<sup>7-9</sup> Even though experimental vaccines do not prevent infection they have been shown to protect most animals from developing the clinical manifestations of initial infection—that is, disease.<sup>7-18</sup> Vaccine induced immunity also reduces the magnitude and duration of virus replication in the genital tract and diminishes the magnitude of the latent infection.<sup>7, 8, 16</sup> Immunised animals that experience subclinical genital infection (that is, replicate HSV in the genital tract but have no evidence of disease) may subsequently develop recurrent genital infections although the frequency of the recurrent infections is much less than in infected animals that were not immunised. In general, experimental animal studies suggest that HSV vaccines may protect humans from developing severe primary genital herpes and may reduce the likelihood that if infected they will experience fewer recurrent infections and be at reduced risk for transmitting virus to a sexual partner, fetus, or newborn infant. It is possible that the limited use of HSV vaccines could facilitate the spread of genital herpes by increasing the number of subclinically infected

individuals. However, it is likely that immunised subjects who become subclinically infected will experience fewer recurrences and shed less virus with each recurrence making these individuals less contagious than infected people who had not received the vaccine. Compared with unimmunised people it is likely that immunised individuals will require exposure to a greater amount of virus in order to become infected, thus making these individuals less likely to acquire infection if exposed to an immunised person who is subclinically infected. If this scenario were correct then the widespread use of HSV vaccines would be predicted to reduce the spread of genital herpes.

While current vaccine strategies seem unlikely to prevent completely the establishment of latent infection it is worth noting that experimental studies have shown that initial genital infection with attenuated HSV mutants induces immune responses that protect the ganglia from becoming infected after genital rechallenge with virulent virus.<sup>19, 20</sup> These results suggest it should be possible theoretically to induce immune responses that can protect against latent infection and thereby obviate the need for a sterilising mucosal immunity. When considering the results of the reinfection experiments it is worth noting that initial genital infection induces local mucosal responses as well as systemic immune responses. For a vaccine to prevent latency or to significantly protect the genital tract it may be necessary to induce as yet undefined mucosal immune responses.<sup>21, 22</sup>

#### HSV vaccines—current status

In the past two decades there have been six types of genital herpes vaccines developed (table 2): inactivated virion derived vaccines; adjuvanted subunit vaccines; vectored vaccines; replication limited live viral vaccines; genetically attenuated live viral vaccines; and nucleic acid vaccines.

Inactivated virion derived vaccines are prepared from HSV infected cell cultures and contain both viral and cellular material. Vaccines may contain nucleic acids and proteins (that is, whole virion vaccines) or may be partially purified so as to contain only proteins or glycoproteins. There are numerous

examples of these types of product including the Skinner vaccine from the United Kingdom,<sup>23 24</sup> the Cappel vaccine from Belgium,<sup>25</sup> and the Merck HSV glycoprotein vaccine from the United States.<sup>26</sup> No inactivated virion derived vaccine has been shown to be effective in well controlled clinical trials.<sup>27 28</sup> No major vaccine company is currently pursuing the development of inactivated virion derived vaccines.

Adjuvanted subunit vaccines consist of one or two HSV proteins combined with newly developed adjuvants. The proteins are produced by recombinant DNA methods and avoid the safety and manufacturing problems associated with use of HSV infected cell cultures.<sup>27</sup> The adjuvants are intended to enhance the immunogenicity of the viral protein(s) inducing broader and more durable immunity. Two companies, Chiron and Smith-Kline Beecham have been pioneers in the development of adjuvanted HSV subunit vaccines. The Chiron vaccine containing HSV-2 glycoproteins B and D combined with MF59, an oil in water adjuvant, was shown to be safe and immunogenic in humans<sup>29</sup> but reportedly failed in two clinical trials to protect volunteers from acquiring genital HSV infection. The details of the trials have not yet been published so the reasons for the failure are unclear. Chiron has abandoned further development of an adjuvanted subunit HSV vaccine. The SmithKline Beecham vaccine consists of HSV glycoprotein D combined with a potent adjuvant, 3-de-O-acylated monophosphoryl lipid A (3d-MPL). The vaccine has been shown to be highly immunogenic<sup>30</sup> and its effectiveness in preventing the development of symptomatic genital herpes is currently being assessed in a large multinational clinical trial. The results of the clinical study are expected by late 1998 or early 1999.

Vectored vaccines consist of an avirulent replication competent viral or bacterial vector that has been engineered to express one or two HSV genes. Numerous vectors have been used to express HSV genes including vaccinia virus, adenovirus, varicella zoster virus, and salmonella.<sup>12 13 31-33</sup> Upon immunisation the vector replicates producing the HSV gene product(s) inducing cellular and humoral immune responses directed against the HSV protein(s). Such vectored vaccines have been shown to be immunogenic and protective in animal model systems<sup>12 13 31-33</sup> but have not yet entered clinical trials.

The replication limited live viral vaccines are genetically engineered mutants that undergo a single replication cycle without producing infectious progeny. Upon immunisation the vaccine virus infects cells and produces an aborted infection that induces both humoral and cellular immune responses. Replication limited live viral vaccines have been shown to be protective in small animal models of genital herpes.<sup>9 17 34 35</sup> The vaccine developed by Cantab Pharmaceuticals has also been shown to be safe and immunogenic in phase 1 clinical trials.<sup>36 37</sup> The Cantab vaccine has been licensed to Glaxo Wellcome and further clinical

development is planned. An American company, VRI, Inc, also has a replication limited live viral vaccine which is in preclinical development.

Genetically attenuated live viral vaccines are replication competent HSV mutants that have had known virulence genes deleted so that they are incapable of causing disease. The concept is appealing because such vaccine viruses should be capable of inducing broad and durable anti-HSV immunity. The difficulty with such vaccines is ensuring that they are indeed avirulent while remaining immunogenic. A genetically attenuated live HSV vaccine tested in animals was shown to be immunogenic and effective against genital herpes<sup>10</sup> but when tested in humans by Pasteur-Merieux was found to be poorly immunogenic. Pasteur-Merieux has discontinued further development but a California based company, Aviron, Inc, has begun preclinical development of genetically attenuated live HSV vaccines.<sup>38</sup>

Nucleic acid vaccines are based on the observation that injection of DNA encoding an immunogenic protein can induce the host to produce humoral and cellular immune responses directed against the encoded protein.<sup>39</sup> Unlike subunit vaccines that predominantly induce humoral responses, DNA vaccines mainly engender cell mediated immune responses. Recent reports have demonstrated that DNA vaccines encoding HSV proteins, mainly glycoprotein B or D, are immunogenic in mice and guinea pigs and protect animals against experimental HSV challenge.<sup>8 15 16 18 40</sup> Several companies including Vical Inc, Merck, and Dynavax have HSV DNA vaccines in pre-clinical development. One company, Apollon Inc, has initiated a phase 1 clinical trial in the United States of its facilitated HSV DNA vaccine.<sup>18</sup> Because nucleic acid vaccines are radically different from other more traditional types of vaccines it will be important to establish the safety of these products in humans. Likewise, it may be necessary to optimise nucleic acid vaccines for human use, thus delaying somewhat their entry into more extensive clinical evaluation.

## Conclusion

The development of a safe and effective vaccine appears to be the only realistic strategy for controlling the problem posed by genital herpes. Several different types of HSV vaccines are currently undergoing preclinical or clinical evaluation making the prospect for success much greater than in previous years. While none of the HSV vaccines presently in development is likely to induce a sterilising immunity it is uncertain that any vaccine can induce immune responses that completely prevent pathogen replication at a mucosal surface. With regard to mucosal HSV infections it is realistic to expect that HSV vaccines will prevent the development of symptomatic genital herpes and reduce or prevent latent infection, thereby diminishing the risk of recurrent infections. Vaccines are likely to afford considerable protection to the immunised individual and prevent many of the con-



sequences of genital herpes listed in table 1. With widespread use there is reason to believe that HSV vaccines might reduce the spread of genital herpes.

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